

degrees of relatedness at the amino acid and nucleotide sequence levels. A number of the pyrogenic toxins include a disulfide loop as a structural feature. The staphylococcal enterotoxins have a disulfide loop, as do some others in this family. Examples of other pyrogenic toxins that have a disulfide loop are the streptococcal superantigen ("SSA") and streptococcal pyrogenic exotoxin A ("SPEA").

The pyrogenic toxins have varying degrees of relatedness which provides the basis for separating some of them informally into subgroups. One subgroup includes staphylococcal type B and C enterotoxins ("SEB" and "SEC"), as well as SPEA and SSA. These toxins share between about 49% to greater than 95% amino acid sequence homology (Reda et al, Infect. Immun., 62:1867-1874: (1994)). Another subgroup of related pyrogenic toxins include staphylococcal type A and E enterotoxins (SEA and SEE) which are 83% homologous to each other (Couch et al, J. Bacteriol., 70:2954-2060 (1988)), less so but significantly to SED (Bayles et al., J. Bacteriol., 171:4799-4806 (1989)). The amino acid sequences of this second subgroup is more distantly related to SEB, SEC, SPEA, and SSA. Examples of pyrogenic toxins having disulfide bonds are present in both of these two subgroups. TSST-1 and streptococcal pyrogenic exotoxins B and C (SPEB and SPEC) are examples of a third subgroup of less related toxins. Although toxins from this third subgroup may share some conserved regions (see table 3) with toxins from the other subgroups, there is little overall sequence homology between toxins in the third subgroup and the pyrogenic toxins in the other two subgroups. Neither TSST-1, SPEB nor SPEC includes a disulfide loop.

The disulfide loop region of a native pyrogenic toxin, such as a native staphylococcal enterotoxin, is generally modified through deletion of a number of amino acid residues within the loop. The modification typically includes deletion of amino acid residues within the disulfide loop region and may include one or more substitutions and/or additions to the remaining loop residues. After modification, the disulfide loop region typically contains no more than about 10 and, preferably, no more than about 6 amino acids residues. In another embodiment of the invention, a modified pyrogenic toxin is formed from a native pyrogenic toxin modified by deletion of at least 40% of the amino acid residues within the disulfide loop region, e.g., by deletion of 8 or more amino acid residues from the disulfide loop region of a native type C staphylococcal enterotoxin.

The present invention is also directed to isolated nucleic acids which include a nucleotide sequence encoding a modified pyrogenic toxin.